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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/730,946	12/10/2003	Takayuki Yoshioka	2003_1801	6300

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WENDEROTH, LIND & PONACK, L.L.P.
2033 K STREET N. W.
SUITE 800
WASHINGTON, DC 20006-1021

EXAMINER	
WALLER, ROBIN REGINA	
ART UNIT	**PAPER NUMBER**
1626	

DATE MAILED: 01/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/730,946	YOSHIOKA ET AL.	
	Examiner	Art Unit	
	Robin R. Waller	1626	

-- The MAILING DATE of this communication appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *preliminary amendment filed 12/22/04*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/10/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Office Action

Election/Restriction

Claims 1 –10 are pending in this application.

Priority

This application claims priority to DIV 10/257,917 dated 10/18/02 US Patent No. 6,720,343 which is 371 of PCT/JP01/03214 dated 04/16/2001 and JP 2000-120234 dated 04/21/2000

Information Disclosure Statement

The information disclosure statement filed 12/10/03 has been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1,5,6 and 8 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Specifically, claim 1 because the specification, while being enabling for inhibition of some metalloproteinases fails to provide for the broad function of inhibiting all

metalloproteinases. This rejection can be overcome by deleting the phrase "for inhibiting matrix metalloproteinases"

Claims 5 and 6 because the specification, while being enabling for diseases treatable by inhibiting matrix metalloproteinases, fails to provide for the broad list of all possible diseases treated by inhibition of matrix metalloproteinases. And which matrix metalloproteinases are affective. This rejection can be overcome by inserting a list of specific diseases and specific matrix metalloproteinases that can be inhibited to treat those diseases as supported by the specifications data and examples.

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

The Nature of the Invention

The nature of the invention in claims 1,5,6 and 8 is treatment of lung cancer by the inhibition of matrix metalloproteinases.

The State of the Prior Art

The state of the prior art is that matrix metalloproteinases are a class of enzymes MMP-1 through MMP-23 (see Specification page 1) secreted by tumor and stromal cells. They are expresses during physiologic processes such as wound repair, reproduction, mammary involution and tissue growth and remodeling. These enzymes are involved in a number a diseases such as atherosclerosis, corneal ulceration, emphysema, osteoarthritis, osteoporosis, rheumatoid arthritis, ulcerative colitis, tumor invasion, and metastasis. It is currently thought that an imbalance between active MMP and TIMP(tissue inhicitors of matrix metalloproteinases) are cause degradation of the basement membrane and allows angiogenesis, tumor growth and invasion to occur. Therefore, synthetic MMP inhibitors are being developed for their potential anti-metastatic and anti-angiogenic properties. (see Lush et al)

The predictability or lack thereof in the art

The instant claimed invention is highly unpredictable as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to therapeutic effects of matrix metalloprotienases related diseases, inhibiting one

type of matrix metalloproteinase may not have the same affect as the inhibition of other metalloproteinases and treating one type of disease related to matrix metalloproteinases may not treat all diseases associated with matrix metalloproteinases.

Hence, in the absence of a showing of correlation between all the diseases claimed as capable of treatment by the pharmaceutical composition of claim 1 and the compounds of claim 2, as well as the inhibition of the particular matrix metalloproteinases, one of skill in the art is unable to fully predict possible results from the administration of the compounds of claim 2 due to the unpredictability of the role of a particular matrix metalloproteinase or which particular disease(s) is treatable by this method.

The nature of pharmaceutical arts is that it involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The amount of direction or guidance present

The direction present in the instant specification is that the pharmaceutical composition of claim 1 and the compounds of claim 2 can inhibit particular matrix metalloproteinases, which will treat lung cancer. However, the specification is silent and fails to provide guidance as to whether treatment for all matrix metalloproteinases mediated diseases, present and future, except for lung

cancer (see Specification pags 1) require the inhibition matrix metalloprotienase i.e. the specification fails to provide a correlation between the all matrix metalloproteinases diseases and the inhibition of all matrix metalloproteinases. Also, the only direction and guidance present is one example, which is for the inhibition of matrix metalloproteinases –2, -8 and -9 for the treatment of lung cancer (see Specification pages 38-42).

The presence or absence of working examples

The only presence of a working example is the example on pages 38-42 for the treatment of mouse lung carcinoma cells. There are not other working examples for any other diseases listed in the specification. Also, the compounds which are disclosed in the specification have no pharmacological data regarding the treatment of any other disease besides lung carcinoma of the mouse and have no data on the possible treatment using all matrix metalloproteinases .

The breadth of the claims

The breadth of the claims is that the pharmaceutical composition of claim 1 and the compounds of claim 2 can treat any matrix metalloprotienase - mediated disease with any matrix metalloproteinase.

The quantity of experimentation needed

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine every diseases that would be benefited by the inhibition of matrix metalloproteinases and would then have to determine whether the claimed compounds would provide treatment of the diseases by the inhibition of all matrix metalloproteinases.

The level of the skill in the art

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Thus, the specification fails to provide sufficient support of the broad use of the pharmaceutical composition of claim 1 and the compounds of claim 2 of for the treatment of all matrix metaloproteianse mediated disease. As a result necessitating one of skill to perform an exhaustive search for which matrix metalloproteinase -mediated diseases can be treated by the pharmaceutical composition of claim 1 and the compounds of claim 2 in order to practice the claimed invention.

Genentech Inc. v. Novo Nordisk A/S (CAFC) 42 USPQ2d 1001 , states that " a patent is not a hunting license. It is not a reward for search , but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which metalloproteinase -mediated mediated diseases can be treated by the compounds encompassed in the instant claims, with no assurance of success.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1, 3,4,5,6,10 is rejected under 112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In claim 1 there is no mention of a carrier. It is suggested by examiner that applicant insert a carrier into claim 1,3, and 4. In claim 5 and 6 the claims lack medical treatment language. It is suggested that applicant insert "administering to a mammal in need thereof a therapeutically effective amount of the compound of claim 1. Claim 3 is a duplicate of claim 1 and should be deleted. Claim 5 lacks antecedent basis for the term "compound". Examiner suggests replacing compound with composition.

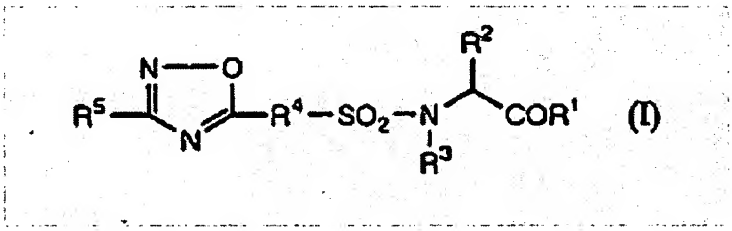
Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claim1-4 are rejected under 35 U.S.C. 102(a) as being anticipated by WO 1999-JP4859 (see WO 200015213).

In claim 2, applicant teach the formula below:



Wherein R1= hydoxy, R2 = lower alkyl or a optionally substituted aryl, R3= H and R5 = aryl optionally substituted on independently selected from F, F3C, H3C, or H3C.

Wantanabe et al., disclose the formula of claim 2 wherein R1 = hydroxyl, R2 is an isopropyl, R3 =H, R4= optionally a methyl . The prior art reads on the compounds of claim 2 lines 1,3 and 5 and clearly anticipated the remainder of the compounds of claim 2 located on lines 2 and 3 wherein the R2=optionally substituted aryl instead of a lower alkyl.

Conclusion

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Robin Waller whose telephone number is (571) 272-2901. Ms. Waller can normally be reached Monday through Friday 8:30AM to 6:00PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mr. Joseph McKane, can be reached at (571) 272-0699.

The fax phone number for the organization where this application or proceeding is assigned is 571- 273-5300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Robin Waller
Patent Examiner
Art Unit 1626, Group 1620
Technology Center 1600

for Kamal Saeed
Joseph McKane
Supervisory Patent Examiner
Art Unit 1626, Group 1620
Technology Center 1600